CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

40301

CORRESPONDENCE

ANDA 40-301

Taro Pharmaceuticals U.S.A. Inc.
U.S. Agent for: Taro Pharmaceuticals Inc.
Attention: Lorraine Sachs
5 Skyline Drive
Hawthorne, NY 10532

MAR 19 1998

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation dated March 16, 1998 and your correspondence dated March 17, 1998.

NAME OF DRUG: Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg

DATE OF APPLICATION: March 2, 1998

DATE (RECEIVED) ACCEPTABLE FOR FILING: March 3, 1998

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Kassandra Sherrod
Project Manager
(301) 827-5849

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

ANDA 40-301
cc: DUP/Jacket
Division File
Field Copy
HFD-610/J.Phillips
HFD-92
HFD-615/M.Bennett

Endorsement: HFD-615/PRickman, Chief, RSB /S/ date 3/19/98
HFD-615/NMahmud, CSO /S/ date 3/18/98
HFD-645/BArnwine, Sup. Chem. _____ date
WP File x:\new\firmsnz\taro\ltrs&rev\40301.ack
FT/njg/3/18/98
ANDA Acknowledgment Letter!

ANDA 40-301

Taro Pharmaceuticals USA, Inc.
Attention: Lorraine W. Sachs
U.S. Agent for: Taro Pharmaceutical Industries, Ltd.
5 Skyline Drive
Hawthorne, NY 10532

AUG 5 1999

Dear Madam:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 of the Federal Food, Drug, and Cosmetic Act for Warfarin Sodium Tablets, USP.

Due to changes in the approved package insert labeling of the listed drug (Coumadin® - DuPont Pharmaceuticals; revised May, 1999; approved July 9, 1999), we ask that you revise your insert labeling in accordance with the enclosed innovator's labeling.

Please revise your labeling at the time of next printing or within 180 days of the receipt of this letter, whichever is sooner, and submit final printed insert labeling as a "Special Supplement - Changes Being Effected" in accordance with 21 CFR 314.70(c) to this approved application.

Sincerely yours,

/S/ 8/4/99

Robert L. West, M.S., R.Ph.
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Enclosure: Coumadin® package insert labeling

labeling review drafted 6/14/99 a. Vega

May 27, 1999

REVIEW COPY

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
N/AF

Reference: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg
Labeling Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted March 2, 1998 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg and to the letter from the Agency on May 26, 1999, in which the following labeling deficiencies were stated:

INSERT

Comment 1:
GENERAL COMMENT

We acknowledge your comment that you have submitted "FPL" labels and labeling but please note that for insert labeling to be in final print the text of the insert must appear on one continuous sheet of paper.

Response:
Please find attached "FPL" insert labeling where the text of the insert is on one continuous sheet of paper.

Comment 2:
PRECAUTIONS

Exogenous Factors - ... with warfarin sodium are ...
(two locations)

CENTER FOR DRUG REC'D MAY 28 1999 OGD EVALUATION AND RESEARCH

Response:
We have corrected the two sentences to read as the Agency requests.

\\TARONY\SYSC\USERS\SUSI\WORD\ANDA\WARFARIN\LETTERS\99sla001.doc
05/27/99 3:14 PM

Comment 3:
DOSAGE AND ADMINISTRATION

Table 3

Lighten the background shading so that the contrast becomes sufficient.

Response:
We acknowledge the comment, and have eliminated the shading – in order to increase the contrast.

Comment 4:
HOW SUPPLIED

There is the statement "Store in carton until contents have been used." present but you have not supplied carton labelling. Please comment.

Response:
This sentence was inadvertently copied from the innovator's insert. We have removed the sentence from our labeling since we are not supplying our product in carton labeling.

Enclosed please find:

- 12 Final Printed Inserts.
- An annotated side-by-side comparison of our proposed labeling with our last submission, with all the differences annotated and explained.

This concludes our response to the Agency's letter of May 26, 1999. If you should have any further questions, or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

Statistical Review: ANDA 40-301, Warfarin Sodium Tablets USP 1, 2, 2.5, 3, 4, 5, 6, 7.5 & 10 mg, Taro Pharmaceuticals USA, Inc.

Material reviewed: one orange-colored volume of ANDA 40-301, volume 6 of 14. Data for my analyses were provided on diskette in data files sent to me by the Office of Generic Drugs.

Surendra P. Shrivastava, Ph.D. is the Division of Bioequivalence reviewer for this submission. The material in this review was previously communicated to Dr. Shrivastava through electronic mail.

The issues in the review involve the sponsor's two-treatment, two-sequence, four-period replicated-crossover BE study (study no. 97-129, Three PK parameters (AUCt, AUCinf, and Cmax) were analyzed.

All PK parameters were statistically analyzed after log-transformation. These log-transformed parameters are designated as LAUCT=ln(AUCt), LAUCINF=ln(AUCinf), and LCMAX=ln(Cmax).

23 subjects (out of 24 subjects enrolled) completed the BE study.

The two treatments studied were:

treatment T - Taro 5 mg tablet, manufactured in Israel (Lot No. 780049, Expiry date: N/A) - dose = 1 tablet

treatment R - DuPont Pharma, USA 5 mg USP crystalline (Coumadin®) tablet, marketed in the USA. (Lot No. ELB048A, Expiry Date: 01-00) dose = 1 tablet

The study was conducted in two groups of subjects. The experimental design and subject numbers for those subjects who completed the study are as follows:

		period			
		1	2	3	4
group 1	sequence 1	**T**	**R**	**T**	**R**
	sequence 2	**R**	**T**	**R**	**T**

		period			
		1	2	3	4
group 2	sequence 1	**T**	**R**	**T**	**R**

subject numbers:

group 1, sequence 1: 1 6 9 10 11 12 13 17 20 21

group 1, sequence 2: 2 3 4 5 7 8 14 15 16 18 19 22

group 2, sequence 1: 23 24

Periods 2, 3, and 4 of group 1 occurred at the same time as periods 1, 2, and 3, respectively, of group 2. There was a two week washout period between periods. Both subjects in group 2 received the treatments in the same sequence.

At the request of Dr. Shrivastava, statistical analyses were carried out for the following subsets of subjects:

all subjects (23 subjects, 92 observations)

subset 1: excluding subject nos. 4, 7, 8, 20, and 21, who had non-zero concentrations in some zero time blood samples (18 subjects, 72 observations)

subset 2: excluding subject nos. 7, 9, 14, and 19, who had Cmax occurring at the first non-zero sampling time (0.25 hours) (19 subjects, 76 observations)

subset 3: excluding subject nos. 4, 7, 8, 9, 14, 19, 20, and 21, the subjects who were excluded in subset 1 and/or subset 2 (15 subjects, 60 observations)

In addition, I carried out analyses for one other subset of subjects:

subset 4: excluding subject 7, period 4
subject 9, period 3
subject 14, period 3
subject 19, period 3

only excluding the specific observations where Cmax occurred at the first non-zero sampling time. For these four observations, AUC's as well as Cmax were excluded (23 subjects, 88 observations)

Statistical Models

The statistical model assumed initially for the analyses was:

$$Y_{ijkl} = \mu_{ijl} + \alpha_i + \gamma_k + \varepsilon_{ijkl}$$

$$\begin{pmatrix} \mu_{ijT} \\ \mu_{ijR} \end{pmatrix} \sim NID\left[\begin{pmatrix} \mu_T \\ \mu_R \end{pmatrix}, \begin{pmatrix} \sigma^2_{BT} & \rho\sigma_{BT}\sigma_{BR} \\ \rho\sigma_{BT}\sigma_{BR} & \sigma^2_{BR} \end{pmatrix}\right]$$

$\varepsilon_{ijkT} \sim NID(0, \sigma^2_{WT})$ and $\varepsilon_{ijkR} \sim NID(0, \sigma^2_{WR})$

where Y_{ijkl} = the response (e.g. ln(AUCt), ln(Cmax), or ln(AUCinf)) for subject j in sequence i receiving treatment l in period k

μ_{ijl} = the average response to treatment l for subject j in sequence i

α_i = the effect of sequence i

γ_k = the effect of period k

ε_{ijkl} = the within-subject random error for subject j in sequence i receiving treatment l in period k

Statistical analyses using this model were carried out using SAS PROC MIXED. For analyses without carryover effects, the SAS statements used initially were:

```
PROC MIXED MAXITER=500;
CLASSES GRP SEQ SUBJ PER TRT;
MODEL <y> = GRP SEQ GRP*SEQ PER PER*GRP TRT;
RANDOM TRT/TYPE=FA0(2) SUB=SUBJ G;
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.10;
```

where <y> is the particular response (LAUCT, LCMAX, LAUCINF) being analyzed. These SAS statements allow for possible subject-by-treatment interaction and also allow the within-subject variances of T and R to differ. This analysis provides an estimated variance-covariance matrix for the subject-specific treatment means. If this estimated variance-covariance matrix was not positive definite (which means that the between-subject correlation between the subject-specific means for T and R was estimated to be 1.0), the statistical model was modified to the following:

$Y_{ijkl} = \mu_l + \alpha_i + s_{(i)j} + \gamma_k + \varepsilon_{ijkl}$

$s_{(i)j} \sim NID(0, \sigma^2_s)$, independently of ε_{ijkl}

where μ_l = the mean in the population for treatment l

$s_{(i)j}$ = random effect of subject j in sequence i

all other terms are as described previously.

The SAS statements used to carry out analyses under this modified model were:

```
PROC MIXED MAXITER=500;
CLASSES GRP SEQ SUBJ PER TRT;
MODEL <y> = GRP SEQ GRP*SEQ PER PER*GRP TRT;
RANDOM SUBJ(GRP*SEQ);
REPEATED/GRP=TRT SUB=SUBJ;
ESTIMATE 'T vs. R' TRT 1 -1/CL ALPHA=0.10;
```

In fact, the estimated variance-covariance matrix was not positive definite in all cases except three: LAUCT and LAUCINF for the all subjects analysis, and LAUCT for the subset 4 analysis.

For analyses with carryover effects in the model, an additional factor was included in the CLASS and MODEL statements to reflect the carryover effects.

Analyses without Carryover Effects

We have carried out analyses of the sponsor's replicated-crossover BE study for all of the indicated subsets of subjects. The resulting 90% confidence intervals (in percentages) for the ratio of test product geometric mean response over reference product geometric mean response are:

	LAUCT	LCMAX	LAUCINF
all subjects	99.59 , 106.19	93.04 , 102.09	99.77 , 107.22
subset 1	99.08 , 103.18	91.24 , 101.38	98.99 , 104.78
subset 2	99.91 , 104.58	90.78 , 99.68	99.17 , 104.73
subset 3	99.97 , 104.62	89.44 , 99.72	98.96 , 105.00
subset 4	99.71 , 105.89	92.77 , 102.02	99.96 , 106.13

For each of the specified subsets of subjects, the 90% confidence intervals fall within the usual limits of 80% to 125% for LAUCT, LAUCINF, and LCMAX.

Analyses with Carryover Effects

Dr. Shrivastava has requested that an analyses be done examining the possibility of unequal carryover effects in this bioequivalence study. This is a legitimate concern given the fact that there was evidence of direct carryover of the drug substance from one study period to the next in several cases (i.e. non-zero Cmin values).

If a treatment administered in a crossover study has an effect on the response to a treatment administered at a later period of the study, this is called a carryover effect. In bioequivalence studies, we have generally assumed that we only need to worry about *first-order* carryover effects - i.e. effects that a treatment has on the response to a treatment administered in the next period. In the design for the bioequivalence study under ANDA 40-301, treatment T is always preceded by treatment R and treatment R is always preceded by treatment T. We therefore only have to worry about two possible carryover effects: the effect that administration of T has on the response to R administered in the next period, and the effect that administration of R has on the response to T administered in the next period. If these two possible carryover effects are not equal, then the estimate of the difference between the average response to T and the average response to R that we would obtain with no carryover effects in the model will be biased. The p-values for the test of this bias are as follows:

	p-values for bias		
	LAUCT	LCMAX	LAUCINF
all subjects	0.2837	0.2335	0.2958
subset 1	0.5674	0.7103	0.4728
subset 2	0.3387	0.5890	0.4294
subset 3	0.4066	0.9958	0.4630
subset 4	0.3325	0.2287	0.3339

In the analysis of bioequivalence studies where the possibility of unequal carryover needs to be considered, it has been the practice to test for bias due to carryover effects and to drop carryover effects from the statistical model if the p-value for such bias is greater than 0.10. If the p-value for bias is less than or equal to 0.10, carryover effects are retained in the statistical model used to make the final inference. In the above table, the p-value for bias is greater than 0.10 in all cases. Nevertheless, at the request of Dr. Shrivastava I have calculated the 90% confidence intervals resulting from analyses using a statistical model that includes carryover effects. These 90% confidence intervals are:

	LAUCT	LCMAX	LAUCINF
all subjects	100.14 , 112.25	93.86 , 116.50	100.20 , 114.80
subset 1	97.82 , 107.65	87.05 , 111.74	97.76 , 111.80
subset 2	99.62 , 110.94	87.98 , 109.76	98.26 , 111.71
subset 3	99.30 , 110.53	83.00 , 107.53	97.73 , 112.39
subset 4	99.71 , 112.50	93.70 , 116.59	99.65 , 114.53

As may be seen, even with carryover effects included in the statistical model the resulting 90% confidence intervals fall within the limits of 80% to 125% in all cases.

Summary

1. With or without carryover effects included in the statistical model, the 90% confidence intervals for the ratio of the average response for treatment T over the average response for treatment R fall within the usual bioequivalence limits of 80% to 125%for all three PK parameters (AUCt, Cmax, and AUCinf), for all of the examined subsets of subjects.

2. Potential bias due to carryover effects was not statistically significant in any case ($p > 0.10$ in all cases).

/S/

Donald J. Schuirmann
Expert Mathematical Statistician
Quantitative Methods & Research staff

/S/ 10/23/98

Concur: Stella Green Machado, Ph.D.
Director, Quantitative Methods & Research staff

cc:
Original ANDA 40-301

HFD-655	Surendra P. Shrivastava
HFD-655	Shriniwas G. Nerurkar
HFD-651	Rabindra N. Patnaik
HFD-650	Dale P. Conner
HFD-601	Gordon R. Johnston
HFD-617	Aida L. Sanchez
HFD-615	Harvey A. Greenberg
HFD-705	QMR Chron
HFD-705	Stella G. Machado
HFD-705	Donald J. Schuirmann

September 22, 1998

TARO

Office of Generic Drugs; CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NDA ORIG AMENDMENT
AC

Reference: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg
Major Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted March 2, 1998 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg.

Reference is also made to your letter dated July 14, 1998, in which we received the following comments:

Comment #1:
We request that you revise the raw material specifications for Warfarin to include USP test <467> for Organic volatile impurities in accordance with the USP monograph.

Response
Organic Volatile Impurities listed in USP <467> (i.e.) are not used in our manufacturing, handling and storage processes of Warfarin Sodium Clathrate drug substance. Enclosed as **Attachment 1.1** (pages S01 through S02) is an official statement that certifies that Taro does not employ any of the above Organic Volatile Impurities in the manufacturing process.

Comment #2:
Please revise the bulk drug specifications for total impurities to % to incorporate the significant figure which is integral to rounding off procedures.

Response
Taro's specifications for Warfarin Sodium Clathrate drug substance which appear on pg. 06513 of the ANDA (included herewith for your convenience as **Attachment 2.1**,

RECEIVED
SEP 24 1998
GENERIC DRUGS

Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

(pages S03 through S04) indicate "Related compounds, Total % - Not more than (1.0%". Therefore, we are assuming that your comment refers to the specification column on the Certificates of Analysis provided for the three batches 780019A, 780022 and 780023.

Enclosed as **Attachment 2.2** (pages S05 through S08) are the revised Certificates of Analysis for batches 780019A, 780022, and 780023. Please note that the most updated Certificates of Analysis for these three batches are provided in **Attachment 3.2** (pages S11 through S14). The additional specifications and test results are discussed in our response to comments 3, 4, and 11.

Comment #3:

We request that you revise the bulk drug specifications to include a specification for particle size distribution.

Response

Particle size distribution of four lots of Warfarin Sodium Clathrate, USP was determined with a Laser particle size analyser. Three of these four lots were used in the production of the exhibition batches of Warfarin Sodium Tablets, USP (Lots: 780023,780022 and 780019A).

The results obtained are summarized in the table below:

Size (μm)	ASTM (Mesh size)	Cumulative % volume of active under			
		780019A	780022**	780023**	780016
38		66.6	75.8	85.2	78.5
45		74.5	82.8	89.6	85.4
53		81.3	88.4	93.1	90.3
63		87.1	93.1	95.6	94.1
75		91.5	96.5	97.2	96.9
90		**94.6**	**98.9**	**98.1**	**99**
106		96.4	99.8	98.7	99.8
125		97.7	100	99.2	100
150		98.6		99.7	
180		99.2		99.9	
212		99.5		100	

** Batch used in the manufacturing of the biobatches

The data show the majority of the particles to be smaller than 100 μm in all four batches. Therefore, a limit of "NLT)% of the particles is smaller than 90μm" would be justified. This limit was now added to the revised release specification sheet given in **Attachment 3.1** (pages S09 through S10). Updated Certificates of Analysis for all three lots of Warfarin Sodium Clathrate used in the production of the exhibition batches, which include particle size distribution results, are given in **Attachment 3.2** (pages S11 through S14).

The method) for particle size determination is given in **Attachment 3.3** (pages S15 through S16).

Comment #4:

We request that you revise the raw material specification for Warfarin to include a specification for bulk and/or tap density.

Response

Bulk density of three lots of Warfarin Sodium Clathrate, USP was determined. These batches were used in the production of Taro's nine exhibition batches. The results are summarized in the table below:

Batch No. Bulk Density	780019A	780022**	780023**
g/mL	0.4	0.3	0.4

** Batch used in the manufacturing of the biobatches

The specification of g/mL is based on the results obtained. The revised specification sheet of Warfarin Sodium Clathrate in **Attachment 3.1** (pages S09 through S10) includes this specification. Please note that we have also updated our drug substance specification by adopting the current USP methods for the Identification tests (instead of Taro's method which is actually a transcription of the former USP methods). Updated Certificates of Analysis for the three batches of Warfarin Sodium Clathrate, USP (780019A, 780022, and 780023) used in the production of the exhibition batches, which include bulk density results, are given in **Attachment 3.2** (pages S11 through S14).

Comment #5:

Regarding the inactive ingredient Lactose Anhydrous NF, please update the tests and specifications in accordance with the changes indicated in USP 23/NF 18 Supplement 8.

Response

Enclosed as **Attachment 5.1** (pages S17 through S18) are Taro's revised specifications for Lactose Anhydrous, NF, written in accordance with the changes indicated in USP 23/NF 18 Supplement 8.

Comment #6:

Regarding the inactive ingredient Magnesium Stearate NF, please provide a certification statement from the manufacturer Merck regarding compliance with the OVI testing requirements listed under USP <467>.

Response

Enclosed as **Attachment 6.1** (pages S19 through S20) please find a statement received from Merck indicating that Organic Volatile Impurities are excluded during manufacturing, handling and storage of Magnesium Stearate, and therefore it complies with the NF specifications and the USP requirements under <467>.

Comment #7:

According to the batch records, no routine in-process controls are performed on the final blend. We request that you establish tests and specifications for content uniformity, tap and / or bulk density and particle size. These tests are essential since this is a low dose drug.

Response

- Content uniformity: We have now adopted the specifications recommended by the current USP of % , and an RSD of not more than .%, for content uniformity of the blend. The analytical method used for testing content uniformity of the blend is provided in **Attachment 7.1** (pages S21 through S27). However, since we have added the Content Uniformity test, we are deleting the test for blend assay, as blend assay can also be calculated from the average of the uniformity results. Therefore, the blend assay specifications are being deleted from the In-process control specification sheet.

- Bulk density : All the final blends of Taro's Warfarin Sodium Tablets, USP exhibition batches were tested for untapped bulk density. The results obtained are summarized in the table below:

Final Blend of Taro's Warfarin Sodium Tablets, USP	Untapped Bulk Density (g/mL)
1 mg (780075)	0.7
2 mg (780100)	0.7
2.5 mg (780095)	0.7
3 mg (780096)	0.7
4 mg (780086)	0.7
5 mg (780049)	0.7
6 mg (780097)	0.7
7.5 mg (780098)	0.7
10 mg (780060)	0.6

The bulk densities of Taro's final blends ranged between g/mL . Based on this data we have decided to set our specification for bulk density of the final blend at ' g/ mL.

- Particle size: We have measured the particle size distribution of the nine final blends of Warfarin Sodium Tablets, USP. The results for 90% of the particles are given in the following table:

Sample No.	90% of Particles smaller than (μm)								
	1 mg (780075)	2 mg (780100)	2.5 mg (780095)	3 mg (780096)	4 mg (780086)	5 mg (780049)	6 mg (780097)	7.5 mg (780098)	10 mg (780060)
1	352	331	331	346	352	339	317	349	337
2	344	343	336	324	341	344	342	328	350

Enclosed as **Attachment 7.2** (pages S28 through S82) are the corresponding complete nine particle size distribution histograms for each lot.

The data indicate that all final blends exhibit a similar particle size distribution, i.e. 90% of the particles are smaller than 352 μm.

Since testing for bulk density and particle size of the blend are inter-related, we will include only the test for bulk density in the in-process specifications.

The reason for this is that we use a ( )formulation for all the strengths of Warfarin Sodium Tablets, USP. The ( )of the various strengths contain the exact same quantities of lactose, starch and magnesium stearate and differ only in the quantities of the coloring agents and the drug substance. Being of such minor quantity in the blend, the influence of these two ingredients on the bulk density and particle size distribution of the blend is expected to be negligible. No significant difference between bulk density and/or particle size of the final blend is expected between different strengths and within several batches of the same strength because:

- The blend predominantly contains excipients of defined suppliers having compendial, and Taro particle size, specifications.
- The particle size and bulk density of the drug substance is now controlled (see response to comments 3 and 4) and its contribution to the blend is negligible.

Taro's revised In-process control specifications are provided as **Attachment 7.3** (pages S83 through S92).

Comment #8:

We request that you specify a range for tablet accountability yield on a revised report form and indicate the yield for each tablet strength.

Response

Information regarding tablets yield obtained for the nine exhibition batches of Warfarin Sodium Tablets, USP manufactured by Taro, is summarized in the following table:

Potency (mg)	Batch No.	Tablets Yield (%) *	Rejected (%)**	Overall Yield(%)
1	780075	96.7	1.6	98.3
2	780100	97.5	0.9	98.4
2.5	780095	91.6	6.9	98.6
3	780096	94.0	2.9	96.8
4	780086	96.0	2.1	98.1
5	780049	96.3	2.7	99.0
6	780097	94.1	4.1	98.2
7.5	780098	95.3	1.7	97.0
10	780060	90.1	7.1	97.2

* Includes quantity of sampling

** Occurred during the set up of the tableting machine.

The overall yield varies from 96.8 to 99.0%. Based on this data we would like to propose a limit of not less than 95% for the overall yield of Warfarin Sodium Tablets, USP (including both good tablets and rejected tablets). Our future experience with larger manufacturing scale and commercial batches will enable us to accumulate additional data and re-evaluate our proposed limit. We will revise our report form for each strength to include the limit of not less than 95% for tablet accountability yield for each strength of Warfarin Sodium Tablets, USP.

Comment #9:

Please provide justification of the significant material loss in the tableting of the 10 mg strength product.

Response

The significant material loss in the tableting of Warfarin Sodium Tablets, USP 10 mg, batch 780060, occurred because of difficulties in maintaining a constant tablet weight during the initial set-up of the tableting machine. A broken punch holding plug was observed and replaced properly. The tableting machine was then set up and proper operation was resumed.

Comment #10:

Please revise the final product specification for content uniformity to include the decimal place as specified in the USP because of its significance to "rounding off " procedures.

Response

Enclosed as **Attachment 10.1** (pages S93 through S102) are Taro's revised release specifications for all strengths of Warfarin Sodium Tablets, USP. These specifications properly indicate that the acceptance limits for content uniformity are 85.0-115.0% with an RSD of not more than 6.0%.

Comment #11:

We request comparative bulk drug assay data for the in-house method versus the regulatory method. In addition, you should also provide a commitment acknowledging that the USP monograph methods are the official regulatory methods and that in the case of a dispute over results of non-compliant samples, the USP methodology and test results will take precedence.

Response

Please note that we have decided to employ analytical method which was used for assaying the drug substance for release purposes, for testing assay and related compounds during stability studies, and for determination of related compounds for release of the drug substance.

This method was properly validated and proven to be stability indicating according to R100 given in **Attachment 12.1** (pages S119 through S159) as part of the response to comment no. 12.

Analytical method was recently revised. The changes are in the standard preparation for determination of related compounds and in the calculation method for determination of related compounds for release purposes. The revised version (Edition 4) is given as **Attachment 11.1** (pages S103 through S111). These changes are editorial in nature and therefore validation report R100 supports also the current version of analytical method We have cross validated analytical method against the USP methods for assay and determination of related compounds in Warfarin Sodium Clathrate. The report (R157) is given as **Attachment 11.2** (pages S112 through S118). Three batches of the drug substance were tested for assay and related compounds using both the compendial analytical methods and analytical method The following table summarizes and compares the results obtained:

				USP method		
	780019A	780022	780023	780019A	780022	780023
% Related Compounds	ND	ND	ND	ND	ND	ND
% Assay	99.3	99.8	99.7	100.3	99.6	99.7

ND = Not Detected ; Limit of Detection = 0.04%

We hereby acknowledge that the methods in the USP monograph are the official regulatory methods, and in case of dispute over results of non-compliant samples, the USP methodology and test results will take precedence.

Comment #12:

We request that you conduct a forced degradation study on the placebo and finished product in order to validate that your analytical method is stability indicating . Samples should be exposed to acid, base, peroxide, heat and UV light. Peak purity of the active ingredient should be demonstrated. A reasonable attempt should be made to identify the major degradants.

Response

Enclosed as **Attachment 12.1** (pages S119 through S159) is report R100.2 which summarizes the validation of analytical methods used for assay and determination of related compounds in the drug product and in the drug substance, respectively. Pages 26 through 39 of the report include the forced degradation studies (exposure to heat, acid hydrolysis, alkaline hydrolysis, oxidation and UV light) conducted on standard (drug substance), placebo and sample (ground tablets). The peak purity of Warfarin was determined by scanning five points of the main peak using the peak purity mode of the diodearray detector. The results demonstrate that no degradants which may interfere with the quantitation of Warfarin in Warfarin Sodium Tablets are formed, and that the Warfarin peak is chromatographically pure under these stress conditions. Therefore, these methods are considered to be stability indicating for quantitative determination of Warfarin and its related compounds.

Comment #13:

Please revise the stability specification for assay to include the decimal place as indicated in the monograph because of its significance to rounding off procedures.

Response

As evident from our stability summary report which was submitted in the original ANDA (see page 07823 of ANDA, also see **Attachment 13.1** (pages S160 through S177) for your convenience) all the assay specifications set by Taro include one decimal place according to the USP monograph. A typographical error occurred when these specifications were transcribed to pages 07816 and 07817. Enclosed as **Attachment 13.2** (pages S178 through S184) are the original pages 07816 and 07817 as well as the revised replacement pages which include the corrections. Enclosed as **Attachment 13.3** (pages S185 through S194) are Taro's current stability specifications for all strengths of Warfarin Sodium Tablets, USP. Please note that the Hardness specifications were revised from kp. This change is due to a trend noted during the ongoing stability studies. Several individual tablets showed hardness values up to kp. This did not affect the other physical or chemical parameters of the tablets (see stability report in **Attachment 13.4** (pages S195 through S219)).

Comment #14:

We request that you include a stability test and specification for isopropyl alcohol. The range should be based on the lower limit of NLT % specified in the USP monograph.

Response

Taro did not initially perform isopropyl alcohol (IPA) testing in the tablets since it is not required by the USP monograph. As per the USP monograph for Warfarin Sodium drug substance, Warfarin Sodium and Warfarin Sodium Clathrate are interchangeable. Taro has selected the Clathrate form as it is the pure form of crystalline drug substance. As requested by the reviewer, Taro has developed a headspace GC test for IPA in Warfarin Sodium Tablets, USP as **Attachment 14.1** (pages S220 through S225), and has included corresponding stability specifications for IPA as **Attachment 13.3** (pages S185 through S194)).

Taro proposes stability specifications of "Not less than % " based on the data given in **Attachment 16.1** (pages S226 through S227), which was generated on Taro's room temperature stability samples pulled at the 12 month time point. These data were generated as per the reviewer's request in comment No. 16 (see response). The proposed stability specifications of "Not less than %" assures that at least % Warfarin in the tablet remains in the Clathrate form during the shelf life of the product.

The isopropyl alcohol in the Clathrate is known to be volatile, and can be easily exchanged by moisture in the packaged tablets or after the package is opened. Therefore, it is justifiable that the stability requirements should be significantly lower than the theoretical requirements. Furthermore, our most current room temperature stability data (see report in **Attachment 13.4** (pages S195 through S219)), which include 12 months data, indicate that the lower than theoretical levels of IPA in the tablet has no influence on all other physical and chemical parameters of the tablet.

Comment #15:

Regarding the stability protocol, the stability sample storage temperatures for room temperature and accelerated testing should be revised to allow for excursions from the target temperature. The OGD recommended storage temperature is the ICH proposed range is Accelerated studies are performed at RH. Please revise the protocol and submit the results for review.

Response

As indicated in our stability summary report which was submitted in the original ANDA (see page 07822, which is provided in **Attachment 13.1** (pages S160 through S177) for your convenience), Taro's stability chambers are in accordance with ICH proposed ranges i.e.:
Long term conditions-
Accelerated conditions-

Enclosed as **Attachment 13.2** (pages S178 through S184) are the revised protocol pages as well as original ANDA pages 07815 through 07817.

Comment #16:

We request that you analyze the stability samples for IPA content and submit the results for review.

Response

As requested by the reviewer, we have analyzed stability samples of Warfarin Sodium Tablets, USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg (see data in tables of **Attachment 16.1** (pages S226 through S227)). These samples were tested at their current time point of 12 months, The method that was developed for this test is given in **Attachment 14.1** (pages S220 through S225). The percent of IPA found, based on the theoretical weight of Warfarin Sodium Clathrate in the tablet, ranged from %. It should be noted that approximately one year ago, there was a sudden unexpected failure in the

stability chamber electrical system which resulted in elevation of temperature in the stability chamber far in excess of 25°C for a period of less than 2 days. Taro retested the Warfarin Sodium Tablets immediately thereafter and found them to meet the then current specifications (which did not, at the time, include a specification for IPA content). Therefore, it was decided to continue the stability program as planned. Taro believes that this excursion would be a "worse case scenario" and therefore did not harm the integrity of our program. We believe that this excursion affected the IPA content, and therefore we also analyzed the retained samples (at room temperature 23° C ±2°C).

As expected, the IPA levels were significantly higher in each batch and package size in the retained samples. Only in one case (1 mg tablets packaged in 100's) the % of IPA was below 8.0. In conclusion, the IPA content found in the stability samples support the proposed stability specification of "Not less than % " (see response to comment 14).

Comment #17:

The stability limit for moisture should be tightened based on the submitted results.

Response

The highest value of % LOD in Warfarin Sodium Tablets observed thus far during the stability study is % (see updated stability summary report on **Attachment 13.4** (pages S195 through S219)). The stability data also show that there is no significant changes in the % LOD over time. Based on the present data, we believe that the stability specification for moisture content measured by loss on drying can be tightened to NMT(%. This limit will provide for any potential increase in moisture that might occur in the future, assuming 24 months shelf life. The revised specification is included in the current specifications sheets of **Attachment 13.3** (pages pages S185 through S194).

Comment #18:

It was noted that the potency in some stability samples significantly deviated from the target of 100.0% (i.e., as low as %) after 3 months at room temperature. Please provide comment.

Response

The deviation from the target of 100.0% was not due to the stability of the product. Some batches of tablets had a potency of less than 100.0% when tested for release. In the example mentioned in the deficiency letter (which probably refers to Batch No. 780049, of 5 mg tablets), the potency of the 5 mg tablets at 3 months room temperature was %, whereas the potency at T-0 was %, which is not significantly different. All other data in the updated stability report of **Attachment 13.4** (pages S195 through S219) show that Taro's Warfarin Sodium Tablets, USP are stable with regard to their potency under accelerated and room temperature conditions.

This completes our response to the Agency's letter of July 14, 1998.

If you should have any further questions, or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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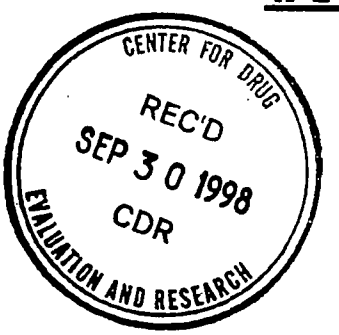
September 29, 1998

FPL

NDA ORIG AMENDMENT

N/AF



Office of Generic Drugs
Food and Drug Administration
Document Control Room
MPN II
7500 Standish Place, Room 150
Rockville, MD 20857

Re: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg
Labeling Amendment

Dear Sir/Madam:

Reference is made to our approved Abbreviated New Drug Application 40-301, submitted under Section 505(j) of the Federal Food, Drug and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg and 10 mg on March 2, 1998.

Reference is also made to a letter from the Agency dated August 31, 1998 in which the following labeling comments were made:

1. *GENERAL COMMENTS:*

   Section 126 of Title I of the FDA Modernization Act of 1997, amends Section 503(b)(4) of the Federal Food, Drug, and Cosmetic Act to require at a minimum, that prior to dispensing, the label of prescription products contain the symbol ***"Rx only"****. A GUIDANCE FOR INDUSTRY entitled "Implementation of Section 126 of the Food and Drug Administration Modernization Act of 1997 - Elimination of Certain Labeling Requirements", was revised July 1998 and posted at Internet site http://www.fda.gov/cder/guidance/index.htm. Please note that Section IV, "Frequently Asked Questions" offers guidance on placement of the symbol on all labels and labeling.*

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GENERIC DRUGS

2. *CONTAINER*

   a. *See general comments.*

   b. *You may delete the statement "Made in Israel". [redundant]*

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c. *We encourage you to differentiate your drug products of different strengths by using contrasting colors (preferably based on the color of the tablet) and/or using boxing, or some other means.*

d. *Please assure that the text on the labels appear clearly legible.*

e. *Revise the storage requirement to read "Store at controlled room temperature 15°- 30°C (59°- 86°F)".*

f. *We note that your have not proposed carton labeling. Delete the statement "STORE IN CARTON...BEEN USED." and/or comment.*

g. *Delete the asterisk following the established name and the text "*Present as crystalline sodium warfarin isopropanol clathrate." from the container labels.*

3. *INSERT*

a. *GENERAL*

i. *Please note that the labeling of the reference listed drug was last approved June 1, 1998. The following comments are based on this latest innovator's labeling. Other editorial comments are also made.*

ii. *Please note that USAN names are common nouns and should be treated as such in the text of labeling (i.e., lower case). Upper case may be used when the USAN name stands alone as on labels or on the title of the package insert.*

iii. *It is preferable to use "2.5 mg" and "7.5 mg" rather than respectively throughout the text as appears on the container labels.*

iv. *Replace with "PT/INR" throughout the text except in the "Laboratory Control" subsection under DOSAGE AND ADMINISTRATION section.*

b. *DESCRIPTION*

i. *First paragraph, second sentence:*

...4-hydroxycoumarin sodium salt and is.....

ii. *First paragraph, last sentence:*

...molecular formula is...[rather than]

iii. *We encourage the inclusion of the molecular weight.*

iv. *Identify the botanical source for starch. [i.e., corn starch]*

v. *Revise to read "Anhydrous lactose" rather than*

c. *CLINICAL PHARMACOLOGY*

i. *Metabolism - Last sentence:*

... the in vivo anticoagulant... [italic]

ii. *Clinical Trials*

A) *Reduce the prominence of the subsection headings of this subsection so that they are differentiated from subsection headings.*

B) *Myocardial Infarction - Table*

(1) *Include title "TABLE 2" in the table.*

(2) *Relocate the items in the first row so that they are aligned with the appropriate columns.*

C) *Mechanical and Bioprosthetic Heart Valves:*

Delete the entire last paragraph.

d. *CONTRAINDICATIONS (Miscellaneous) - Revise to read as follows:*

... anesthesia, malignant hypertension and known hypersensitivity to warfarin or to any other components of this product.

e. *WARNINGS*

i. *Replace "Warfarin Sodium Tablets, USP" with "warfarin" throughout the text.*

ii. *Third paragraph:*

... hemorrhage, necrosis, and/or gangrene is present.

iii. *Include the following subsection heading and text immediately preceding the seventh paragraph "A severe elevation...".*

Heparin-induced thrombocyopenia: *Warfarin should be used with caution in patients with heparin-induced thrombocytopenia and deep venous thrombosis. Cases of venous limb ischemia, necrosis, and gangrene have occurred in patients with heparin-induced thrombocytopenia and deep venous thrombosis when heparin treatment was discontinued and warfarin therapy was started or continued. In some patients sequelae have included amputation of the involved area and/or death (Warkentin et al, 1997).*

iv. *Seventh paragraph:*

Delete the last sentence "This has been...".

v. *Lactation*

A) *First sentence:*

Warfarin appears...

B) *Last sentence - Revise to read as follows:*

Infants nursed by mothers treated with warfarin sodium had no change in prothrombinn times (PTs). Effects in premature infants have not been evaluated.

vi. *Miscellaneous - Fourth paragraph:*

...failure may exhibit greater than expected PT/INR response to warfarin sodium, thereby requiring more frequent laboratory monitoring, and reduced doses of warfarin sodium.

vii. *Fifth paragraph:*

Concomitant use... [rather than "Concurrent use..."]

f. *PRECAUTIONS*

i. *See comment (i) under WARNINGS.*

ii. Print the first four paragraphs in bold face type.

*iii. Fourth paragraph - The following factors, alone or in combination, may be responsible for **INCREASED PT or INR** response: Exogenous Factors:*

A) Include the following classes in the list of "classes of drugs" in the appropriate places based on the alphabetical order.

5-lipoxygenase Inhibitor, Antiandrogen, Leukotriene Receptor Antagonist, Selective Serotonin Reuptake Inhibitors

B) Relocate the following classes in the list of "classes of drugs" to be in alignment with the left margin.

Hepatotoxic Drugs, Tuberculosis Agents, Uricosuric Agents

C) Include the following drugs in the list of "specific drugs reported" in the appropriate places based on the alphabetical order.

azithromycin, fluoxetine, flutamide, fluvoxamine, zafirlukast, zileuton

D) Relocate the followings in the list of "specific drugs reported" to the appropriate places based on the alphabetical order.

vitamin E, warfarin overdose, valproate

E) Relocate the following classes in the list of "specific drugs reported" to be in alignment with the left margin.

olsalazine, oxaprozin, oxymetholone valproate, vitamin E, warfarin overdose

*iv. Fifth paragraph - The following factors, alone or in combination, may be responsible for **DECREASED PT or INR** response: Exogenous Factors:*

Include "6-mercaptopurine" in the list of "specific drugs reported" after "meprobamate".

v. Information for Patients - Add the following in bold face type as the last sentence in this subsection:

Patients should be informed that all warfarin sodium, USP, products represent the same medication, and should not be taken concomitantly, as overdosage may result.

g. ADVERSE REACTIONS

i. See comment (i) under WARNINGS.

ii. Revise the fifth paragraph to read as follows:

Adverse reactions reported...purple toes syndrome, hepatitis, cholestatic hepatic injury, jaundice, elevated liver enzymes, vasculitis, edema, fever, rash, dermatitis, including bullous eruptions, urticaria, abdominal pain including cramping, flatulence/bloating, fatigue, lethargy, malaise, asthenia, nausea, vomiting, diarrhea, pain, headache, dizziness, taste perversion, pruritis, alopecia, cold intolerance, and paresthesia including feeling cold and chills.

h. OVERDOSAGE

See comment (1) under WARNINGS.

i. DOSAGE, ADMINISTRATION, AND LABORATORY CONTROL

i. Revise the section heading to read "DOSAGE AND ADMINISTRATION".

ii. In addition to the general comment (iv) under INSERT, revise the terms "the INR and/or PT ratio" to read "PT/INR". [two incidences]

iii. First paragraph:

... particular patient's PT/INR response to the drug. The dosage should be adjusted based upon the patient's PT/INR (See...)

iv. Venous Thromboembolism (including pulmonary embolism) - Include the following as the last sentence:

In patients, with risk factors for recurrent venous thromboembolism including venous insufficiency, inherited thrombophilia, idiopathic venous thromboembolism, and a history of thrombotic events, consideration should be given to longer term therapy (Schulman et al, 1995 and Schulman et al, 1997).

v. Atrial Fibrillation:

Delete the last sentence.

vi. *Include the following subsection immediately prior to the "Laboratory control" subsection:*

Intravenous Route of Administration: *Warfarin sodium for injection provides an alternate administration route for patients who cannot receive oral drugs. The IV dosage would be the same as those that would be used orally if the patient could take the drug by the oral route.*

vii. *Laboratory Control*

A) *Revise the prominence of this subsection heading to be consistent with other subsection headings.*

B) *First paragraph, fourth and penultimate sentences:*

Replace "PT" with "PT/INR".

C) *First paragraph, last sentence - Revise to read as follows:*

...interchanged with warfarin sodium tablets, USP, as well as whenever other medications are initiated, discontinued, or taken irregularly (See PRECAUTIONS).

D) *Last paragraph:*

... is shown in Table 3.[5] [rather than "Table 2"]

E) *Table 2:*

Revise to read "Table 3".

vii. *Treatment During Dentistry and Surgery - Fifth Sentence:*

..., dental and minor surgical procedures...

j. *HOW SUPPLIED*

i. *We note that the color descriptions of the 3 mg and 5 mg strengths are not consistent with your Controls for Finished Dosage Form statements. Please revise accordingly and/or comment.*

ii. *We note that the engraving description of the 2 mg, 2.5 mg, 3 mg, 6 mg, and 7.5 mg are not consistent with your Controls for Finished Dosage Form statements. Please revise accordingly and/or comment.*

iii. *Penultimate paragraph:*

..., as described in the above table, ...
[rather than "previous"]

iv. *See comments (d) & (e) under CONTAINER.*

v. *See GENERAL COMMENTS.*

With respect to these comments, please note that we have made the corrections and enclosed herein please find:

12 - Final Printed Labels
4 - Draft Package Inserts

Also enclosed, please find a side-by-side comparison annotating the changes that have been made. This concludes our response to the Agency Labeling Amendment letter dated August 31, 1998.

Sincerely,

Lorraine W. Sachs
Associate Director, Regulatory Affairs

October 21, 1998

ORIG AMENDMENT
N/AC

TARO

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Reference: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg
Amendment to a Major Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted March 2, 1998 under Section 505 (j) of the Federal Food, Drug, and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg and to our Major Amendment submitted September 22, 1998.

In our Major Amendment submission, we included copies of our current In-Process Control Specifications on pages S83 through S92 as part of our response to Comment 7. However, subsequent to our submission, we discovered that the specifications which we sent to you did not contain the correct limits for bulk density of)g/mL, as we indicated in our written response to Comment 7. Therefore, we have revised these Specifications to contain the correct bulk density limits and we are submitting them at this time.

We apologize for any inconvenience this may have caused. If you should have any further questions, or require additional information, please do not hesitate to contact the undersigned at (914) 345-9001.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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Taro Pharmaceuticals U.S.A., Inc. Five Skyline Drive, Hawthorne, NY 10532 Tel: 914-345-9001 Fax: 914-345-8728 http://www.taropharma.com

October 21, 1998

Center for Drug Evaluation and Research
Central Document Room
12420 Parklawn Drive
Room 2-14
Rockville, MD 20852

Attention: Associate Director, FDA, Office of International Programs

Reference: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg
Amendment to a Major Amendment

Dear Sir/Madam:

Taro Pharmaceutical Industries Ltd. hereby submits and certifies that the enclosed field copy is a true copy of the technical information provided in the above referenced amendment.

If there are any questions in regards to this documentation, please do not hesitate to contact the undersigned.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314 & 601)

Form Approved : OMB No. 0910-0338
Expiration Date: April 30, 2000
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
TARO PHARMACEUTICAL INDUSTRIES LTD.	10/21/98
TELEPHONE NO. *(Include Area Code)* 914 345-9001	**FACSIMILE (FAX) Number** *(Include Area Code)* 914 345-8728

APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued)*	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE
14 HAKITOR STREET HAIFA BAY, ISRAEL 26110 FCIS026	TARO PHARMACEUTICALS U.S.A., INC. 5 SKYLINE DRIVE HAWTHORNE, NY 10532 (914) 345-9001 PHONE (914) 345-8728

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER (If previously issued) 40-301

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)* WARFARIN SODIUM TABLETS, USP

PROPRIETARY NAME *(trade name)* IF ANY N/A

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(If any)* 3-(-ACETONYLBENZYL)-4-HYDROXYCOUMARIN

CODE NAME *(If any)* N/A

DOSAGE FORM: TABLETS

STRENGTHS: 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 MG

ROUTE OF ADMINISTRATION: ORAL

(PROPOSED) INDICATION(S) FOR USE: ANTICOAGULANT

PPLICATION INFORMATION

PLICATION TYPE (check one)

☐ NEW DRUG APPLICATION (21 CFR 314.50) ☒ ABBREVIATED APPLICATION (ANDA, AADA, 21 CFR 314.94)

☐ BIOLOGICS LICENSE APPLICATION (21 CFR part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☐ 505 (b) (1) ☐ 505 (b) (2) ☐ 507

IF AN ANDA, OR AADA, IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug COUMADIN TABLETS Holder of Approved Application DUPONT PHARMA, USA

TYPE OF SUBMISSION (check one)

☐ ORIGINAL APPLICATION ☒ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION

☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ SUPAC SUPPLEMENT

☐ EFFICACY SUPPLEMENT ☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

REASON FOR SUBMISSION ADJUSTMENT OF AMENDMENT DATED SEPTEMBER 21, 1998

PROPOSED MARKETING STATUS (check one) ☒ PRESCRIPTION PRODUCT (Rx) ☐ OVER-THE-COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED _____ THIS APPLICATION IS ☒ PAPER ☐ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION

Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

OCT 22 1998

oss References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs and DMFs referenced in the current application)

5/5/99 FA acted, forwarded for review. ① To Labeling Reviewer ② To CMC Reviewer for review.

April 30, 1999

TARO

NDA ORIG AMENDMENT
N/FA

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

Re: ANDA 40-301
Warfarin Tablets USP, 1, 2, 2.5, 3, 4, 5, 6, 7.5, and 10 mg
Facsimile Amendment

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted on March 2, 1998 under Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Warfarin Sodium Tablets USP, 1 mg, 2 mg, 2.5 mg, 3 mg, 4 mg, 5 mg, 6 mg, 7.5 mg, and 10 mg.

Reference is also made to your letter dated April 13, 1999 in which the following deficiencies were stated:

A. Chemistry Deficiencies

1. **Regarding (testing, we request that you expand your specification to state that the mean of individual sample results should lie within % with a standard relative deviation (RSD) of %.**

Response 1

We acknowledge the Agency's chemistry deficiencies and we hereby commit to make the appropriate change to our in-process specifications. The specifications are as follows:

Individual:	%
Mean:	90.0 – 110.0%
RSD:	%

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B. Bioequivalency Comments

1. The dissolution testing should be conducted in 900 mL of water, at 37°C using USP Apparatus 2 (Paddle) at 50 rpm. The test product should meet the following specifications:

Not less than __% (Q) of the labeled amount of the drug in the dosage form is dissolved in 30 minutes.

Response 1

We acknowledge the Agency's bioequivalency comments and we commit to incorporate the indicated dissolution method and specifications in our stability and quality control programs.

C. Labeling Deficiencies

1. INSERT

a. GENERAL

i – ii. .....

b. WARNINGS

i. – ii. .....

c. PRECAUTIONS

i. – iii. .....

d. ADVERSE REACTIONS

i. – ii. .....

e. OVERDOSAGE

See comment (i) under PRECAUTIONS.

f. DOSAGE AND ADMINISTRATION

i. – vi. .....

Please revise your package insert labeling, as instructed above, and submit in final print.

Response

We acknowledge the Agency's labeling deficiencies and have made the appropriate corrections. Enclosed please find:

- 12 final printed package inserts

Also enclosed, in accordance with 21 CFR 314.94 (a) (8) (iv), please find a side-by-side comparison of our insert submitted today, with our previoulsy submitted insert along with the difference annotated.

This concludes our response to the Agency letter of April 13, 1999.

If you should have any questions, please contact the undersigned.

Sincerely,

Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

March 2, 1998.

TARO

Mr. Douglas Sporn
Office of Generic Drugs
CDER, Food & Drug Administration
Metro Park North
7500 Standish Place, Room 150
Rockville. MD 20855

Re: Original Abbreviated New Drug Application (ANDA) for Warfarin Sodium Tablets USP, 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg

Dear Mr. Sporn:

In accordance with the provisions of Section 505(j) of the Federal Food, Drug and Cosmetic Act and Section 314.94 of 21 CFR, and on behalf of the applicant, Taro Pharmaceutical Industries Ltd., located at Bet Merkazim, Maskit St. P.O.B 2043, Herzlia Pituach 46120, Israel, Taro Pharmaceutical USA Inc. (applicant's US Agent) located at Five skyline Drive, Hawthorne, NY 10532, USA, submits an original Abbreviated New Drug Application (ANDA) seeking approval to market in the USA, Warfarin Sodium Tablets USP, 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg strengths that are bioequivalent to the listed drug, Coumadin Tablets, manufactured by Dupont Pharma at Wilmington, Delaware 19880, pursuant to NDA N0 9218.

Taro Pharmaceutical Industries Ltd., developed and manufactured both the drug substance, Warfarin Sodium, USP and the drug product, Warfarin Sodium Tablets, USP.

If you have any comments or questions regarding this ANDA, please contact the undersigned at 5 Skyline Drive, Hawthorne, Ny 10532, Tel. (914) 345-9001 ext.282.

Sincerely,

for Lorraine Sachs, RAC
Taro Pharmaceuticals Inc.,
Regulatory Affairs Department
Associate Director

/ic
Enclosure: 41 Books and 3 diskettes

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GENERIC DRUGS

Warfarin Sodium Tablets USP, 1, 2, 2.5, 3, 4, 5, 6, 7.5, 10 mg

Clarification points relevant to the ANDA

Please note the following clarification points relevant to this ANDA:

-Taro Pharmaceutical Industries Ltd performs all of its manufacturing at the company's Haifa Bay plant, the Active raw material Warfarin Sodium Clathrate USP and the finished product Warfarin Sodium Tablets USP,1 ,2 ,2.5, 3, 4, 5, 6, 7.5, 10mg are manufactured at its Haifa Bay facility (DMF

-Documents in the ANDA were prepared in Israel where a day/month/year dating convention is used ie July 8, 1996 is written as 08.07.96 as opposed to the US dating of 07.08.96. Such dating convention is used throughout the manufacturing and quality control documents.

-The original language for most of the documents herein is Hebrew. All documents written in Hebrew, or any language other than English, have been translated into English on the page or the page that immediately follows the Hebrew version. It should be noted that, as with text, tabular information in the Hebrew language runs right to left on the printed page. English translations of the table, however, run left to right.

-For the purpose of clarity some of the original documents have been retyped. The retyped version follows the original document.

-Taro's exhibit batch size is)tablets. The proposed scale-up batch size is) tablets. Master Formulas for intended commercial production batches are included in this ANDA.

TARO PHARMACEUTICALS INC.
130 EAST DRIVE
BRAMALEA, ONTARIO
L6T 1C3

March 17, 1998

NEW CORRESP
NC

Office of Generic Drugs, CDER
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, M.D. 20855-2773

Reference: **ANDA 40-301**
Warfarin Sodium Tablets USP, 1, 2, 2,5, 3, 4, 5, 6, 7.5, 10 mg
New Correspondence

Dear Sir/Madam:

Reference is made to our Abbreviated New Drug Application submitted under Section 505(j) of the Federal Food, Drug, and Cosmetic Act for the above referenced product dated March 2, 1998.

Reference is also made to a telecon of March 16, 1998 between Mr. Nasser Mahmud, FDA, and Lorraine Sachs, Taro Pharmaceuticals USA, Inc., in which a revised Statement of Composition was requested to clearly indicate the quantities of Warfarin Sodium in our formulation.

As per the Agency's request, the quantitative composition statement (pages 6490 and 6491) has been revised to include the Warfarin Sodium equivalents of Warfarin Sodium Clathrate in each strength and copies of the revised pages are hereby provided.

This response is being submitted in two copies. A form FDA 356h is also attached.

If there are any questions regarding this documentation, please do not hesitate to contact the undersigned or our U.S. agent,

Taro Pharmaceuticals U.S.A., Inc.
5 Skyline Drive
Hawthorne, New York 10532
(914) 345-9001
Attn: Lorraine W. Sachs, RAC
Associate Director, Regulatory Affairs

Sincerely,
Taro Pharmaceuticals Inc.

for Derek Ganes, Ph.D.
VP, Regulatory Affairs

/L. Ogbaghebriel

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TELEPHONE
905-791-8276
1-800-268-1975
VOICE MAIL
905-791-5181
TELEFAX NO.
905-791-5008